VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

147

Guidance for Industry

Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (90-Day) Toxicity Testing VICH GL31

The objective of this guidance is to establish recommendations for an internationally harmonized 90-day repeat-dose testing

Comments and suggestions regarding the document should be submitted to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should be identified with the Docket No. 02D-0368.

For questions regarding this document, contact Louis T. Mulligan, Center for Veterinary Medicine, (HFV-153), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-6984, e-mail: lmulliga@cvm.fda.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
November 12, 2003

GL31 (SAFETY: REPEAT-DOSE (90-DAY) TOXICITY)
October 2002
For implementation at Step 7 - Final

STUDIES TO EVALUATE THE SAFETY OF RESIDUES OF VETERINARY DRUGS IN HUMAN FOOD: REPEAT-DOSE (90-DAY) TOXICITY TESTING

Recommended for Implementation
on October 2002
by the VICH Steering Committee

THIS GUIDANCE HAS BEEN DEVELOPED BY THE APPROPRIATE VICH EXPERT WORKING GROUP AND WAS SUBJECT TO CONSULTATION BY THE PARTIES, IN ACCORDANCE WITH THE VICH PROCESS. AT STEP 7 OF THE PROCESS THE FINAL DRAFT IS RECOMMENDED FOR ADOPTION TO THE REGULATORY BODIES OF THE EUROPEAN UNION, JAPAN AND USA.

REPEAT-DOSE (90-DAY) TOXICITY TESTING

TABLE OF CONTENTS

REPEAT-DOSE (90-DAY) TOXICITY TESTING

This guidance represents the agency's current thinking on establishing the safety of veterinary drug residues in human food. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statute(s) and/or regulation(s). If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

1. INTRODUCTION

1.1. Objective of the guidance

A variety of toxicological evaluations are performed to establish the safety of veterinary drug residues in human food. The objective of this guidance is to establish recommendations for internationally harmonized 90-day repeat-dose testing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

1.2. Background and scope of the guidance

The current guidance is one of a series of guidances developed to facilitate the mutual acceptance of safety data for the determination of acceptable daily intakes (ADIs) for veterinary drug residues in human food. This guidance was developed after consideration of the current practices for evaluating veterinary drug residues in human food in the European Union, Japan, United States, Australia, New Zealand, and Canada.

Although this guidance recommends a framework for 90-day toxicity testing of veterinary drugs, it is important that the design of the tests remain flexible. It is recommended that tests be tailored to adequately establish the dose-response and a no-observed adverse effect level (NOAEL) for toxicity following 90-day compound treatment.

1.3. General principles

Adequate toxicity testing should include an assessment of the effects of repeated exposure to a parent compound and/or metabolites. It should also ascertain a dose that does not produce toxicity. As with other types of toxicity testing it is recommended that available information on the compound be utilized in designing the test. Repeat-dose toxicity tests should be performed in sensitive/appropriate species. While species selection should take account of relevance to human metabolism, pharmacokinetics and pharmacodynamics, the generally accepted default species recommended are the rat and the dog. It is recommended that exposure begin early enough in life to encompass

the growth phase of the test animals. In general, the highest dose should be sufficient to produce toxicity. The data obtained from this test may be used to establish a NOAEL for a veterinary drug.

2. GUIDANCE

2.1. Repeat-dose (90-day) toxicity test

2.1.1. Purpose

It is recommended that repeat-dose (90-day) toxicity testing be performed in a rodent and a non-rodent species in order to (1) identify target organs and toxicological endpoints, (2) provide information that will help the setting of dose levels to be used in repeat-dose (chronic) toxicity testing, and (3) identify the most appropriate species for subsequent repeat-dose (chronic) toxicity testing. A NOAEL should be identified from the results of each repeat-dose (90-day) toxicity test.

2.1.2. Experimental design for a 90-day toxicity test

It is recommended that repeat-dose (90-day) toxicity tests be conducted in accordance with OECD Test Guidelines 408 "Repeated Dose 90-day Oral Toxicity Study in Rodents"[1] and 409 "Repeated Dose 90-day Oral Toxicity Study in Non-rodents."[2]

2.1.2.1. Pathological examination

It is recommended that gross necropsy and histopathological examination be performed in accordance with Organization for Economic Cooperation and Development (OECD)Test Guidelines 408[1] and 409[2] with the following exception: for non-rodents, histopathological evaluations should be made on a standardized set of tissues plus gross lesions from all animals in all groups.

3. REFERENCES

1. OECD. 1998. Test Guideline 408. Repeated Dose 90-day Oral Toxicity Study in Rodents. In: OECD Guidelines for the Testing of Chemicals. Organisation for Economic Cooperation & Development, Paris.

2. OECD. 1998. Test Guideline 409. Repeated Dose 90-day Oral Toxicity Study in Non-rodents. In: OECD Guidelines for the Testing of Chemicals. Organisation for Economic Cooperation & Development, Paris.